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Reaction time in healthy elderly is associated with chronic low-grade inflammation and advanced glycation end product

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ABSTRACT

Chronic inflammation and Advanced Glycation End products (AGE) are associated with sarcopenia. Decreased voluntary muscle activation and increased antagonist coactivation can contribute to age-related muscle weakness. The influence of chronic inflammation and AGE in these neuromuscular mechanisms is not clear. We studied whether a relation exists between circulating levels of inflammatory cytokines and AGEs as well as the interplay between agonist and antagonist muscle activation. We studied 64 community-dwelling old subjects, during a maximal isometric voluntary contraction (MVC) and a reaction-time (RT) test of the upper limb. Twenty-five circulating inflammatory biomarkers were determined. Linear regression showed significant relationships between chronic inflammation and six muscle activation parameters. MIP-1β showed a significant negative relation with antagonist coactivation (during MVC) and antagonist muscle activity during pre-movement time (PMT) and movement time (MT) (during RT). A higher level of pentosidine (AGE) was predictive for a longer PMT. We conclude that in older relatively healthy persons antagonist muscle activation is influenced by chronic inflammation, contributing to age-related muscle weakness. Our results also suggest a mechanical and inflammatory influence of pentosidine in upper limb slowing of movement. These findings show novel insight in underlying mechanisms of age-related muscle weakness.

1. Introduction

A chronic low-grade inflammatory profile (CLIP) is seen in most aging people (Krabbe et al., 2004; Roubenoff, 2007). Changes in body composition and decline of the immune system are underlying in complex relationships (Jo et al., 2012; Wilson et al., 2017). It is well known that CLIP is associated with muscle weakness (Beenakker et al., 2010; Beyer et al., 2012) and frailty (Wilson et al., 2017). Since evidence showed that age-related loss of muscle strength is only weakly associated with the reduction in muscle mass (Clark and Manini, 2008; Delmonico et al., 2009; Mitchell et al., 2012) it is accepted that neuromuscular mechanisms, contribute to age-related muscle weakness (Clark and Manini, 2008; Clark and Manini, 2012). However the explanatory mechanisms are not yet fully understood. Neuromuscular mechanisms supposed to be involved are a deficit in voluntary muscle activation and increased antagonist muscle coactivation. The involvement of chronic inflammation in these mechanisms is not clear.

Another factor contributing to the aging process is the low turnover of collagen, resulting in susceptibility to interact with metabolites, allowing the accumulation of non-enzymatic glycation crosslinks, which are irreversible and cause tissue stiffness (Avery and Bailey, 2006; Semba et al., 2010b). Higher levels of these crosslinks, i.e. Advanced Glycation End products (AGE) are independently related to decreased walking abilities, inferior Activities of Daily Living (ADL), decreased muscle properties (strength, power, mass) and increased physical frailty (Drenth et al., 2016). Besides forming of crosslinks, AGE increase oxidative stress and inflammation, through binding with one of the cell surface Receptors for Advanced Glycation End products (RAGE) (Basta, 2008; Uribarri et al., 2007). This activation of RAGE leads to an exacerbation of decreasing muscle strength and physical performance

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(Dalal et al., 2009; Semba et al., 2010a; Semba et al., 2010b). The involvement of AGE in voluntary muscle activation is unclear.

We recently found an association between circulating cytokines and contractile muscle properties (twitch force) during a fatigue protocol, in healthy community dwelling elderly (Arnold et al., 2017). In another study we provided evidence for the presence of an early antagonist muscle coactivation in community-dwelling elderly during a reaction time (RT) test, using fast dynamic movements (Arnold et al., 2015). From a mechanical point of view, this early antagonist coactivation may counteract the agonist muscle, resulting in delay in start of the movement, longer RT and reduced net force production. Our previous findings led to the purpose of this study, which is to answer the question if a relation exists between circulating levels of inflammatory cytokine and AGE and the interplay between muscle activation of agonist and antagonist. Changes in this interplay might be underlying in age-related muscle weakness.

2. Methods

2.1. Participants

This study extends our previous investigations where participants and measurement procedures have been described in detail (Arnold et al., 2015; Bautmans et al., 2011). Here data from sixty-four community-dwelling elderly (32 males and 32 females, aged respectively 79.6 ± 4.1 and 79.6 ± 4.9 years) were analysed (see Table 1). They were recruited via the University community, seniors associations, poster and flyer advertisements, and mailings. Subjects were excluded when presenting functional disability of the dominant upper extremity (paresis/paralysis, tremor or recent surgery), cognitive decline (Mini Mental State Examination (MMSE) score < 24/30 (Folstein et al., 1975), neurologic disorders, acute or uncontrolled conditions, or chronic inflammatory pathology. Stable morbidity was not an exclusion criterion per se (Ferrucci et al., 2004). None of the participants was involved in a specific training program or was a trained master athlete. The study was approved by the Medical Ethics Committees of the Universitair Ziekenhuis Brussel (Belgium) and the Erasmus Universitair Medisch Centrum Rotterdam (The Netherlands); and all participants gave written informed consent.

Table 1
Participants characteristics.

Characteristic	Female (N = 32)	Male (N = 32)
Age (years)	79.6 ± 4.9	79.6 ± 4.1
MMSE (score 0–30)	28.6 ± 1.6	28.6 ± 1.4
bADL-dependency (score 8–32)	8.3 ± 0.5	8.3 ± 0.6
iADL-dependency (score 9–27)	26.6 ± 0.7†	25.3 ± 2.3
YPAS-ADS (score 0–177)	51.9 ± 39.1	47.3 ± 25.3
MVC-triceps/agonist (N)	117.7 ± 39.2†	156.9 ± 49.0
Medication (number)	2.6 ± 3.0	2.6 ± 1.9
Co-morbidity* (number)	1.3 ± 1.4	1.9 ± 1.5
PMT (ms)	310.6 ± 39.6	311.5 ± 43.2
MT (ms)	302.8 ± 73.3†	252.5 ± 64.8
RT (ms)	618.6 ± 89.2†	571.8 ± 77.0

Mean ± SD; † = significant different from male ($p < 0.05$, independent t-test); MMSE = Mini-Mental-State examination; bADL & iADL = respectively basic and instrumental activities of daily life; YPAS-ADS = Activity Dimensions Summary score of the Yale Physical Activity Survey; MVC = maximal voluntary contraction; N = Newton, PMT = pre-movement time; MT = movement time; RT = total RT; *Stabilized (chronic) conditions including hypertension, chronic heart failure, diabetes type-2, chronic obstructive pulmonary disease, osteoarthritis, antecedents of cancer, antecedents of depression, elevated cholesterol.

2.2. Measurements

2.2.1. Clinical characteristics

Height and weight were measured, and self-reported morbidity and medication use were recorded. All participants completed the Yale Physical Activity Survey (YPAS) questionnaire and the Activity Dimensions Summary score (YPAS-ADS) was calculated, reflecting the subject's physical activity (vigorous activity, leisure walking, moving, standing and sitting) over the last month on a scale from 0 (no activity at all) to 177 (maximal activity) (Dipietro et al., 1993). For descriptive purposes dependency for basic activities of daily life (bADL) was rated using a 6-item scale as described by Katz et al. (1963), complemented by orientation in time and place. Each item was scored from 1 (completely independent or no problem ins orientation) to 4 (completely dependent or completely disoriented). Dependency for instrumental ADL (iADL) was evaluated using a 9-item questionnaire following Lawton et al. (1982)). Each item was scored from 1 (completely dependent) to 3 (completely independent). Cognitive functioning was assessed using the Mini Mental State Examination (MMSE) (Folstein et al., 1975). MMSE-scores > 23/30 were considered as normal.

2.2.2. Circulating markers of inflammation and AGEs

Serum levels of 25 different cyto-/chemokines were measured simultaneously by multiplex bead immunoassay (Human Cytokine Twenty-Five-Plex, Biosource International, Nijvel, Belgium) according to the manufacturer's indications, including: IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, CCL2/(MCP-1), CCL3/(MIP-1α), CCL4/(MIP-1β), CCL5/(RANTES), CCL11/(Eotaxin), CXCL9/(MIG), CXCL10/(IP-10), TNFα, IFN-α, IFN-γ, and GM-CSF. Two different AGEs were measured; Pentosidine en CarboxyMethylLysine (CML). Full names and sensitivities are reported in Table 2. Data for samples below the detectable range were imputed as 1 decimal value below the detection limit. When > 50% of the samples were below the detection limit, the marker was excluded for statistical analysis (see Table 2).

2.2.3. Measurement sequence

First, serum was collected by venepuncture from the non-dominant arm and was frozen at −20 °c for later simultaneous determination of circulating cytokines and AGEs. Next, participants' characteristics were assessed and the subjects performed a maximal isometric voluntary contraction (MVC) test of elbow flexion and extension, described by Bautmans et al. (2011), in order to calculate the antagonist coactivation. After 5 min. of recovery the participants performed a RT test (Arnold et al., 2015; Bautmans et al., 2011) which was preceded by a familiarization session (consisting in 15 trials). Both test setups are described in detail in the supplementary material.

2.2.4. Surface electromyography and signal processing

Self-adhesive pre-gelled electrodes (Ag/Cl, 10 mm diameter, 20 mm inter-electrode distance) were placed over the M. Biceps Brachii Caput Breve, M. Triceps Brachii Caput Longum and one reference electrode on the spinal processes of the seventh cervical vertebra (the skin was cleaned using pure alcohol and shaved when necessary) according to the SENIAM-recommendations (Hermens et al., 2000). sEMG sensors were connected to a universal amplifier (MPAQ, IDEE/Maastricht Instruments, Maastricht, The Netherlands) using shielded wires in order to avoid movement artefacts. All raw sEMG signals were simultaneously sampled at 12,500 Hz (Butterworth 4th order, band-pass 10–5000 Hz and notch-filtered) and stored on a personal computer.

Signal processing was performed using data-acquisition software (IdeeQ version 2.9b3, IDEE/Maastricht Instruments, Maastricht, The Netherlands). For the RT-test, 28 stimuli were generated by the test device. When errors occurred (i.e. when movement time > 3 s) the system automatically generated a replacement stimulus. Additionally, an observer recorded the wrongly executed trials during the RT-test

Table 2
Circulating markers of inflammation.

Cyto/chemokine	sensitivity	N=64	
pg/mL		Undetectable (N)	Median ± IQR
IL-1β	<15	39	14.9±24.1
IL-1RA	<20	7	210.0±256.0
IL-2	<15	47	14.9±0.1
IL-2R	<40	1	192.0±103.0
IL-4	<5	23	6.0±8.1
IL-5	<5	61	4.9±0.0
IL-6	<5	35	4.9±6.1
IL-7	<25	54	24.5±0.0
IL-8	<3	2	36.5±32.8
IL-10	<3	23	3.0±3.1
IL-12	<6	-	144.0±73.3
IL-13	<6	41	5.9±23.1
IL-15	<25	41	24.5±9.0
IL-17	<20	49	19.9±0.0
GM-CSF	<5	41	4.9±57.1
TNF-α	<5	54	4.9±0.0
IFN-α	<25	12	40.0±34.5
IFN-γ	<2	33	1.9±3.1
MCP-1	<8	-	520.0±322.5
MIP-1α	<15	8	34.5±27.8
MIP-1β	<10	4	90.5±83.5
RANTES	<20	-	>1100
Eotaxin	<5	-	85.5±58.8
MIG	<20	20	66.5±105.1
IP-10	<5	-	35.0±29.5
Pentosidine (ng/ml)	<0.8	2	7.2±17.2
CML*	<16	2	135.2±122.4

pg/ml = picogram per milliliter; ng/ml = nanogram per milliliter; * = $N = 54$; IQR = interquartile deviation calculated as P75-P25; IL = interleukin; IL-1RA = IL-1 receptor antagonist; GM-CSF = granulocyte macrophage colony-stimulating factor; TNF-α = tumor necrosis factor alpha; IFN = interferon; IL-2R = IL-2 receptor; IP-10 = interferon γ-inducible protein 10; MCP = monocyte chemoattractant protein; MIG = monokine induced by interferon gamma; MIP = macrophage inflammatory protein; RANTES = Regulated up-on Activation Normal T-cell Expressed and Secreted; CML = carboxymethyllysine; When > 50% of samples in the group was below the detection limit (shaded) the cyto/chemokine was excluded for statistical analysis.

(e.g. when the subject missed the target pushbutton or made aberrant movements with the arm). The correctly executed trials were confirmed by offline visual inspection of the accelerometer signals. For each participant, at least 23 correctly executed trials (stimuli) were available for data analysis.

2.2.5. Muscle activation measures

In this study, the outcome variables were muscle activation measures that in previous studies showed a relation with slowness of movement. Here we investigated 1) antagonist coactivation, calculated from data obtained during the maximal isometric voluntary contraction (MVC), 2) RT, 3) pre-movement time (PMT), 4) movement time (MT), 5) antagonist activity during PMT and 6) antagonist activity during MT, 7) antagonist muscle activation time relative to stimulus onset (PMAT) and 8) antagonist muscle activation relative to movement onset (MAT). Muscle parameters 2 to 8 were calculated from data obtained during the RT test. Measurement procedures and calculations are described in the supplementary material. See Fig. 1 and the list of abbreviations for an additional explanation of the measures.

2.3. Statistical analysis

Data were analysed using IBM Statistical Package for the Social Sciences (SPSS version 24.0). Differences in clinical characteristics according to gender were analysed using independent *t*-test. Inflammatory cytokines and AGEs were log(10)-transformed prior to analyses to approximate the normality assumption. Multiple stepwise linear regression was used to determine significant predictor variables that produced the best model for RT measures. Gender, cytokines and AGEs were used as independent variables and eight different muscle activity measures as dependent outcome variables. Potential interaction effects with sex were examined entering all significant factors into the regression model. Cook's distance (> 1) and standardized residuals (> 4) were checked to determine if cases might be influencing the regression models. Significance was set a priori at $p < 0.05$.

3. Results

No significant difference was found between female and male in age, MMSE-score, basic dependency scores, physical activity level, number of medications, number of co-morbidities and pre-movement time (see Table 1). Female showed significant higher instrumental dependency scores, but men showed no problematic scores. As expected females showed a significant longer MT and RT than males.

As can be seen in Table 2, IL-1β, IL-2, IL-5, IL-6, IL-7, IL-13, IL-15, IL-17, GM-CSF, TNF-α and IFNγ levels were below the detection limit in > 50% of the subjects.

3.1. Antagonist coactivation

Coactivation of the antagonist (M. Biceps) during agonist (M. Triceps) MVC was related to female gender, log MIP-1β and log IL-1RA accounting for 31% of the variability. Female showed higher coactivation. No interaction effect of cytokines and female gender was found.

3.2. Reaction time

Regression analysis showed log transformed pentosidine to correlate ($\beta = 0.017$, $\Delta R^2 = 0.06$) significantly with PMT (see Table 3). 24% of the variability in PMT can be predicted by the cytokine pathway expressed by a positive correlation with log IP-10 and a negative correlation with log IL-1R (see Table 3). MT was significantly correlated with female gender and log MIG in which log MIG explains 8%. No relation was found between cytokines or AGEs and RT. Female showed longer MT. No interaction effect of cytokines, pentosidine and female gender was found.

3.3. Antagonist muscle activity

Muscle activity of the antagonist during PMT and MT showed significant negative associations with log MIP-1β ($\beta = -4.648$ and –4.763 respectively) whereas female showed higher muscle activity. No interaction effect of cytokines and female gender was found.

3.4. Antagonist muscle activation time

No relation was found between cytokines or AGEs and the activation time of the antagonist during the pre-movement-time (PMAT). Activation time of the antagonist related to movement onset (MAT) showed a significant negative association with log IL-2R ($\beta = -0.053$, $R^2 = 0.123$).

4. Discussion

This exploratory study for the first time shows the relation between the chronic low-grade inflammation profile (CLIP), reflected by

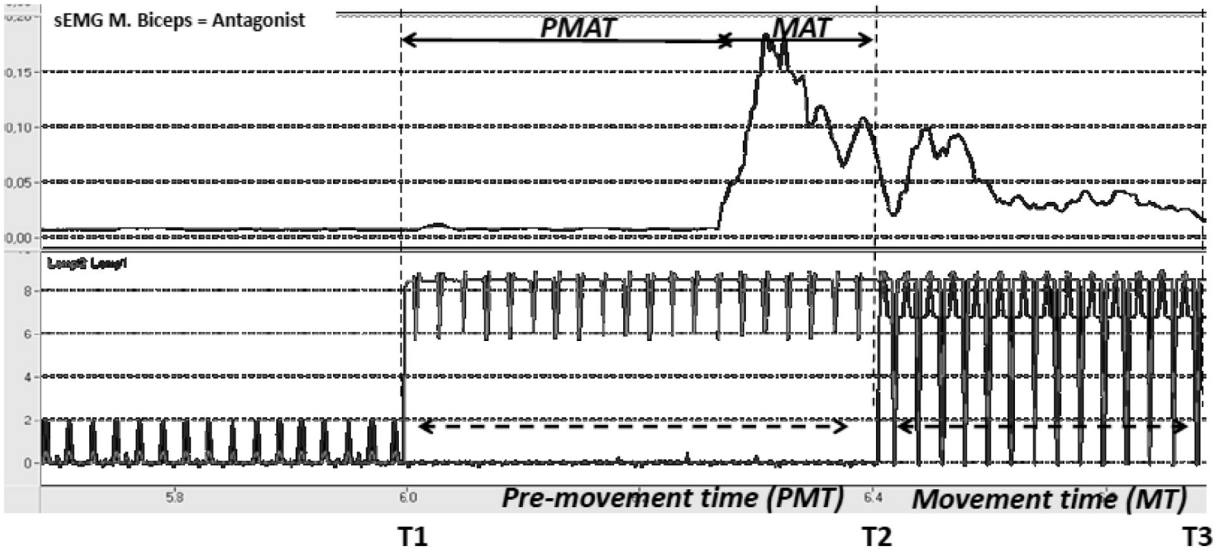

Fig. 1. Signal plot during reaction time test. Plot of sEMG of antagonist muscle (Mm. Biceps) (for illustrative purposes full-wave rectified and RMS-smoothed over 2 ms) and signals of the pushbuttons during a single RT-stimulus in a female participant aged 85 years. T1 = illumination of target pushbutton (visual stimulus, start of PMT i.e. processing time), T2 = participant releases the central pushbutton (end of PMT and start of MT), T3 = participant presses the target pushbutton (end of MT). PMAT = pre-movement activation time, MAT = movement activation time.

Table 3
Relationships between cytokines, AGEs and muscle parameters.

Independent variables	Dependent variable	
	β	R^2
	Antagonist coactivation	
(Constant)	33.534**	0.312
Female gender	9.850**	
Log MIP-1β[a]	−21.075**	
Log IL-1RA[a]	11.363*	
	Pre-movement time (PMT)	
(Constant)	0.231***	0.301
Log IP-10	0.083***	
Log IL-1RA	−0.030**	
Log pentosidine	0.017*	
	Movement-time (MT)	
(Constant)	0.171***	0.216
Female gender	0.054**	
Log MIG[a]	0.046*	
	Antagonist activity during PMT	
(constant)	12.724**	0.230
Female gender	4.883**	
Log MIP-1β[a]	−4.648*	
	Antagonist activity during MT	
(Constant)	14.061***	0.274
Log MIP-1β[a]	−4.763**	
Female gender	3.662**	
	Antagonist activation during MT	
(Constant)	0.190***	0.123
Log IL-2R	−0.053*	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; p-values are two-sided; R^2 = for model.
[a] No interaction with female gender.

inflammatory cytokines, and different muscle activation parameters, probably contributing to slowing of muscle performance. The most noticeable finding was the significant negative relation between MIP-1β and 1) coactivation of the antagonist muscle during an isometric MVC and 2) muscle activity of the antagonist muscle during PMT and MT during a fast dynamic contraction, i.e. the RT test. In addition, a higher level of pentosidine seems to be predictive for a longer PMT.

Markers of chronic low grade inflammation were significantly related with the degree of antagonist coactivation during maximal voluntary isometric contraction, especially MIP-1β and IL-1RA with respectively a negative and a positive association. These associations show the involvement of chronic inflammation in peripheral antagonist muscle coactivation during an isometric MVC. Our previous research has already shown the correlation between contractile properties (twitch force) of the M. adductor pollicis (acting as agonist muscle) and MIP-1β and IL-1RA during an isometric contraction in a population of relatively healthy elderly (Arnold et al., 2017). MIP-1β proteins mediate their biological function by binding to cell receptors and induce intracellular effects leading to chemotaxis, degranulation and phagocytosis. Thus they play a key role in the induction and modulation of inflammatory responses (Maurer and von Stebut, 2004). MIP-1β also plays a key-role in muscle regeneration following muscle injury, due to intensive resistance exercise (Mathers et al., 2012; Yahiaoui et al., 2008). IL-1RA is a cytokine receptor acting as cytokine binding protein, which can down regulate the effects of circulating cytokines (anti-inflammatory). Cytokine receptors tend to have longer half-lives than their target cytokines, and as their secretion appears to parallel that of the cytokine, they are good markers of chronic cytokine activity (Morley and Baumgartner, 2004). Coactivation has been found to be higher in older adults compared to younger persons, during isometric contractions (Izquierdo et al., 1999; Macaluso et al., 2002; Rozand et al., 2017). However studies regarding the influence of aging on antagonist coactivation during isometric contractions in the upper limb, by comparing young and old subjects, show contrasting results (Klass et al., 2007). The negative association between MIP-1β and antagonist coactivation in our participants most probably indicates an impairment mechanism, since the major function of antagonist muscle activation in elderly is to add to joint stabilization, as a compensatory mechanism (Hortobagyi and Devita, 2006; Klein et al., 2001). Here we found an effect of gender on coactivation of the antagonist muscle, indicating a higher level of coactivation in females than males. Gender differences during isometric contractions have been described related to accuracy of movement and antagonist coordination (Brown et al., 2010; Yoon et al., 2009), however the tasks performed in those studies were different. The gender difference might be explained by the lower mean muscle strength in females compared to men, suggesting that the higher coactivation is used as a compensation strategy for maintaining joint stabilization, during isometric contractions.

PMT and MT, together reflecting RT, also showed significant positive associations with the cytokines IP-10 and MIG, and IL-1RA showed

an inverse relation with PMT. In addition, pentosidine showed a positive association with PMT. Both findings suggest that either by the chronic inflammatory- or by the AGE-pathway PMT may be influenced. Although the contribution of pentosidine in predicting PMT was small, this was in line with our initial hypothesis that accumulation of cross-linking AGE would contribute to slowing of muscle function. Our finding confirms the research by Haus et al. (2007) who showed that glycation-related cross-linking of intramuscular connective tissue may contribute to altered muscle force transmission and decreased muscle function in healthy aging elderly, explained by changes in the endomysial collagen tissues (Haus et al., 2007). The stiffness of passive collagen tissues seems to hinder processing time. From a mechanical point of view increased muscle activity of the antagonist gives resistance to the agonist to generate force and the time to start the movement, resulting in decreased force output and delay of the start of the movement. Apparently CML, which is a non-cross-linking AGE, can be considered less influential on the biomechanics of muscle tissue. Our findings in previous research showed that the antagonist muscle activity during PMT was significantly higher compared to the muscle activity in young people (Bautmans et al., 2011). Here also an inverse association was found between the antagonist muscle activity during PMT and MT and the pro-inflammatory marker MIP-1β. The association means that more inflammatory response, reflected by MIP-1β, is related to lower antagonist muscle activity. This negative association probably indicates an impairment of antagonist coactivation during dynamic movements in elderly and in fact indicates an impairment of the joint stabilizing mechanism. The effect of gender on muscle activity during PMT and MT might be related to lower muscle strength and rate of force development (RFD) known in females compared to males (Wu et al., 2016) during dynamic contraction.

Previous work showed that additional to the higher muscle activation of the antagonist, the recruitment time of the antagonist during the RT test of the upper limb (expressed as movement activation time (MAT)), is longer in elderly compared to young participants (Arnold et al., 2015). Here we found no association between CLIP and antagonist PMAT (i.e. the time necessary for stimulus reception, integration and decision-making in the central nervous system, preparation of the motor program, and sending motor commands to the muscles) and a negative association between IL-2R (a cytokine receptor) and MAT. This association accounts only for 12% of the variability in antagonist MAT. Several authors described age-related changes in activation and inhibition patterns at the cortical level in elderly influencing the delay of muscle activation (Bernard and Seidler, 2012; Burke and Kamen, 1996; Heetkamp et al., 2014; Papegaaij et al., 2014). Our findings suggest that CLIP, as another mechanism, is involved in altered muscle recruitment patterns in elderly.

The complex interrelation and mediating role of inflammation-related markers and its association with declining muscle quality and physical functioning has been known for many years (Calvani et al., 2017; Peake et al., 2010). Cytokines that affect muscle function can be produced in the muscle intrinsically or by neutrophils, macrophages, fibroblasts, vascular smooth muscle cells and vascular endothelium (Zoico and Roubenoff, 2002). In addition, also senescent cells can contribute to low-grade inflammation, by an increase in the secretion of pro-inflammatory cytokines which has been defined as the senescence associated secretory phenotype (SASP) (Davalos et al., 2010; Sikora et al., 2014). In our study we determined the most prominent SASP-related biomarkers, including IL-8, IL-6, IL-1, MCP-1, eotaxin and MIP-1α (related to MIP-1β) (Davalos et al., 2010). Since our participants were relatively healthy and well-functioning, we expected that high-sensitivity C-reactive protein (hs-CRP) - a common marker of inflammation which is used frequently in clinical practice to identify patients with chronic inflammation - would be very low in most subjects. Therefore, we choose not to determine hs-CRP, but a large set of cyto/chemokines including both pro- and anti-inflammatory biomarkers. It is beyond the scope of this study to explain the individual function of each factor. More information about muscle protein degradation pathways related to cytokine elevations can be found in the review of Saini et al. (2009). Our findings show that in healthy elderly CLIP is involved in voluntary activation and coactivation of the antagonist, and should motivate clinicians to consider it as targets for therapeutic interventions. The more because exercise as a strong anti-inflammatory strategy has been proven to be effective (Mathur and Pedersen, 2008; Pedersen and Saltin, 2015).

Our findings show positive as well as negative relationships between the inflammatory markers and muscle activity. The interplay between pro-inflammatory cytokines (negative relations with MIP-1β, IP-10, MIG, IL-2R) and anti-inflammatory ones (positive relations with IL-1RA) in our regression model, suggest that a balance between pro- and anti-inflammatory signaling is involved in muscle activity.

The relationship between the antagonist muscle activation parameters and cytokines and AGEs has not been investigated before. Exploring the possible relationships between the complex interrelated cytokines and AGEs, and the muscle outcomes of interest by using the regression method revealed relations contributing to age-related changes in muscle activation.

Pentosidine was included as an independent predictor together with inflammatory cytokines. Since AGE's can have both a mechanical and inflammatory action on muscle performance, the impact of pentosidine on slowing of movement might have been underestimated. Probably this was not the case as no significant correlations between the cytokines and pentosidine were found, which legitimates to interpret pentosidine as an independent variable in the model.

Since the presence of stable comorbidities was not an exclusion criterion per se, it cannot be excluded that other factors related to chronic disease or treatment might have influenced muscle performance in our participants. However, the number of medication was very low, with a mean of 2.6. All participants were free of functional limitations in the dominant arm. It is well known that cholesterol-reducing medication such as statins can have adverse effects including myalgia (Iwere and Hewitt, 2015). However only six subject (< 10%) used statins and none reported muscle pain. Therefore, it is very unlikely that our results were affected by statin use. By allowing participation of subjects with stable chronic conditions we were able to recruit a representative sample of well-functioning older adults and thus our results are more likely to be generalizable than when we would have selected older persons completely free of any comorbidity and medication use. In our study, neither number of medications nor comorbidities showed significant relationships with muscle activity outcomes (data not shown). However, the impact on muscle performance of chronic conditions and commonly used medication at older age merits further investigation.

The scores of the YPAS-ADS also have been entered in the regression models as a covariate. The result showed the subject's physical activity level to be predictive for movement time. Lower activity level was associated with longer movement time. However, the association must be interpreted as negligible ($\beta = -0.001$, $p = 0.016$).

Research in this domain allows qualifying a sample size of 64 as “a high number”. However, given the large number of variables in the study, we cannot completely exclude that some associations – although statistically significant -were identified by chance. This first exploration should therefore be followed by research in a larger sample in order to confirm the relationships. However, the number of independent predictors retained in the regression models were restricted to 3 or less, thus the sample size of our study is likely to be sufficient (at least $n = 20$ per predictor) to obtain valid analyses. The relatively high mean age (79.6 years) of our elderly participants suggests that age-related changes in the neuromuscular system have taken place, thus the sample size is representative, contributing to the relevance of our findings.

5. Conclusions

We can conclude that regression analysis showed significant relationships between circulating cytokines and AGE (pentosidine) and muscle activation parameters during isometric MVC and fast dynamic contractions of the upper arm muscles in community-dwelling elderly. These findings are the first to provide evidence for the involvement of the chronic low-grade inflammatory profile in antagonist muscle activation, contributing to age-related muscle weakness. The results also suggest a mechanical and inflammatory influence of the cross-linking AGE, pentosidine, in slowing of movement. More research is necessary to determine causal relations. However our results show novel insight in underlying mechanisms of age-related muscle weakness and likely contribute to developing more targeted interventions, aimed at countering muscle weakness in elderly.

Abbreviations

RT Reaction Time: pre-movement time + movement time (msec.)
PMT pre-movement time: time for stimulus processing (msec.)
MT movement time: time for motor response completion (msec.)
Antagonist coactivation M. Biceps muscle activation during M. Triceps contraction, as a percentage of the maximal M. Biceps activation during MVC
Antagonist activity during PMT M. Biceps average muscle activation during pre-movement time, expressed as percentage of activation during MVC
Antagonist activity during MT M. Biceps average muscle activation during movement time, expressed as percentage of activation during MVC
Antagonist PMAT M. Biceps muscle activation time relative to stimulus onset (msec.)
Antagonist MAT M. Biceps muscle activation time relative to movement onset (msec.)
IP-10 interferon gamma inducible protein 10
IL-1RA interleukin 1 receptor antagonist
IL-2R interleukin 2 receptor
MIG monokine induced by interferon gamma
MIP-1β macrophage inflammatory protein-1β

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Conflict of interest statement

The authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2018.04.002.

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